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#13

**NOTICE OF APPEAL FROM THE EXAMINER TO
THE BOARD OF PATENT APPEALS AND INTERFERENCES**

Docket Number (Optional)

3523/2/US

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Signature Mary Katriadakis
Typed or printed name Mary Katriadakis

In re Application of
Sandra M. Sims

Application Number 09/933,366 Filed August 20, 2001

For Solution Composition of a Oxazolidinone Antibiotic, etc

Art Unit 1614 Examiner Muirhei, C.

Applicant hereby **appeals** to the Board of Patent Appeals and Interferences from the last decision of the examiner.

The fee for this Notice of Appeal is (37 CFR 1.17(b))

\$ 320.00

- ☐ Applicant claims small entity status. See 37 CFR 1.27. Therefore, the fee shown above is reduced by half, and the resulting fee is:
- ☐ A check in the amount of the fee is enclosed.
- ☐ Payment by credit card. Form PTO-2038 is attached.
- ☐ The Director has already been authorized to charge fees in this application to a Deposit Account. I have enclosed a duplicate copy of this sheet.
- ☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. 19-1025. I have enclosed a duplicate copy of this sheet.
- ☐ A petition for an extension of time under 37 CFR 1.36(a) (PTO/SB/22) is enclosed.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

- ☐ applicant/inventor.
- ☐ assignee of record of the entire interest.
See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed.
(Form PTO/SB/96)
- ☒ attorney or agent of record.
- ☐ attorney or agent acting under 37 CFR 1.34(a).
Registration number if acting under 37 CFR 1.34(a) _____

Karen B. King
Signature
Karen B. King
Typed or printed name
847-581-6996
Telephone number
April 30, 2003
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.191. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: Sandra M. Simms) DOCKET NO.: 3523/2/US
SERIAL NO.: 09/933,366) GROUP ART UNIT: 1614
FILED: August 20, 2001) EXAMINER: Cybille Delacroix Muirhei
TITLE: SOLUTION COMPOSITION OF AN OXAZOLIDINONE ANTIBIOTIC
DRUG HAVING ENHANCED DRUG LOADING

CERTIFICATE OF MAILING

I hereby certify that this document and accompanying documents referred to herein are being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Mail Stop AF, U.S. Patent and Trademark Office, Alexandria, Virginia 22313-1450 on April 30, 2003.

Mary Katriadakis
Mary Katriadakis

Commissioner for Patents
P.O. Box 1450
Mail Stop AF
U.S. Patent and Trademark Office
Alexandria, VA 22313-1450

Sir:

PETITION FOR EXTENSION OF TIME

Applicant hereby petitions for an extension of time of one month to respond to an Office Action mailed December 31, 2002, in prosecution of the above-referenced patent application. A shortened statutory time period for response of three months was set by the Office Action. In connection with this petition, please charge \$110.00 or the sum required under 37 C.F.R. §1.17(a)(1) to Deposit Account No. 19-1025.

NOTICE OF APPEAL

Applicant will file a Notice of Appeal to the Board of Patent Appeals and Interferences, under 35 U.S.C. §134 and fee required under 37 CFR § 1.17(b), on this same date. A copy of the Notice of Appeal is transmitted herewith.

05/07/2003 JADD01 00000104 191025 09933366

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REPLY TO A FINAL REJECTION OR ACTION, UNDER 37 C.F.R. §1.113

Applicant respectfully submits the following reply and a Declaration by Dr. Walter Morozowich, Under 37 C.F.R. § 1.132 (hereinafter, the "Morozowich Declaration"), in response to an Office Action, mailed December 31, 2002, made "final" therein. Applicant respectfully requests entry of the Morozowich Declaration and consideration of the following remarks, under 37 C.F.R. §1.113.

I. REMARKS

Claims 1-30 are pending in the present application. Applicant does not propose to amend any of the claims herein. However, Applicant respectfully requests entry of the following remarks and of the Morozowich Declaration as presenting evidence that rebut the only remaining ground for rejection of the present pending claims, set forth in a previous Office Action, dated August 20, 2001, and sustained in the present Office Action.

A. Rejection of Claim 12, Under 35 U.S.C. § 112

A rejection of claim 12, under 35 U.S.C. § 112, second paragraph, as being indefinite, set forth in the previous Office Action, was withdrawn in the present Office Action, in response to Applicant's response to the previous Office Action. Applicant thanks the Examiner for acknowledging withdrawal of this ground of rejection on page 2, in paragraph 2, of the present Office Action.

B. Rejection of Claims 1-30, under 35 U.S.C. §103(a), over U.S. Patent No. 5,688,792

("Barbachyn *et al.*") in view of U.S. Patent No. 5,646,294 ("Bartroli *et al.*")

This same rejection was set forth in the previous Office Action. Applicant responded to the rejection by submitting a response that included legal arguments, supported by evidence from a Declaration by Dr. Michael Barbachyn, Under 37 C.F.R. § 1.132, demonstrating that a *prima facie* case of obviousness, under 35 U.S.C. § 103(a) had not been set forth in the previous Office Action. Specifically, Applicant demonstrated that neither the Barbachyn *et al.* nor Bartroli *et al.*, nor knowledge generally available to one of ordinary skill in the art would have suggested or motivated one to combine the reference teachings to make the pharmaceutical compositions of the present invention, or to practice the methods of the present invention.

The present Office Action states that the arguments and evidence of nonobviousness presented therein were not found to be persuasive because "it is not clear how the statements in

Applicant's declaration serve to evidence unexpected results." (present Office Action, p. 4, beginning on line 4). However, as noted above, the Barbachyn Declaration was presented as evidence of lack of motivation to combine or modify the teachings of the two cited reference, evidence that a *prima facie* case of obviousness had not been established. Applicant respectfully submits that evidence of unexpected results is one of the indicia of nonobviousness that can be used, if present, as a basis for one of many different arguments for rebutting a *prima facie* case of obviousness. Rebuttal arguments and/or evidence need not be presented where a *prima facie* case of unpatentability, under 35 U.S.C. § 103(a) has not been presented. Applicant submits that such a *prima facie* case has not been established in the present case, for reasons set forth in Applicant's preceding Amendment and Request for Reconsideration, Under 37 C.F.R. § 1.111, submitted August 29, 2002, and in the Barbachyn Declaration submitted therewith.

Alternatively, if a *prima facie* case of obviousness over the two references cited above has somehow been established, Applicant respectfully rebuts any such case by submitting the Morozowich Declaration and the following remarks as evidence of surprising and unexpected results. Applicant respectfully submits that such evidence of nonobviousness must be considered, when present. As stated in the Manual of Patent Examining Procedure ("M.P.E.P."): Applicant submits that such evidence of unexpected or superior results must be considered objective evidence of non-obviousness, when present:

"Affidavits or declarations containing evidence of criticality or unexpected results, commercial success, long-felt but unsolved needs, failure of others, skepticism of experts, etc, must be considered by the examiner in determining the issue of obviousness of claims for patentability under 35 U.S.C. 103." M.P.E.P. 716.01(a).

The Morozowich Declaration demonstrates the unpredictable nature of solubilization of various molecules by cyclodextrins. In the Morozowich Declaration, Dr. Morozowich begins by reviewing and agreeing with evidence, set forth in the Barbachyn Declaration, that given what was known at the time the invention was made with respect to the physical characteristics of cyclodextrins and the hydrophobicity of molecules likely to be solubilized by cyclodextrins, one would not have expected oxazolidinones, with low log P values between about 0 to -2 to be solubilized by cyclodextrins. (Morozowich Declaration, paragraph 3). Dr. Morozowich goes on to cite additional evidence, from the literature, of solubility expectations based upon the structure

of cyclodextrins, in paragraph 7 of the Morozowich Declaration. He also provides the chemical structure and known log P values for a number of different oxazolidinone antibiotic drugs, in Table 1 of the Declaration. (Paragraph 7).

Dr. Morozowich also presents comparison solubility and log P value data of a number of different drugs in either or both of two different cyclodextrins, sulfobutyl- β -cyclodextrin ("SBCD") and hydroxypropyl- β -cyclodextrin ("HPCD") in Table 2 of the Declaration. He observes that linezolid was shown to have a log P value of -0.92, and a solubility of 86 mg/ml in a 500 mg/ml solution of HPCD, while the solubility of nitrofurantoin, with a similar log P value of -0.63, was not increased in the presence of the same concentration of HPCD. (Morozowich Declaration, paragraph 8). Dr. Morozowich concludes this same paragraph by stating that:

"The fact that oxazolidinones are solubilized at all by cyclodextrins is surprising and unexpected, in view of the fact that the oxazolidinones have log P values of 0 to -2, and in view of the fact that nitrofurantoin, with a log P value in the same range, is not solubilized." Morozowich Declaration, paragraph 8.

Dr. Morozowich goes on to note that the degree to which oxazolidinones are solubilized compared to other compounds is also surprising and unexpected. (Morozowich Declaration, paragraph 9). Example 1 and 6 of the present application are cited as illustrating the surprisingly high degree of solubilization undergone by oxazolidinones in the presence of cyclodextrins. (*Id.*) Data presented in Table 2 of the Declaration is also cited as providing evidence of surprising and unexpectedly high solubilities of oxazolidinones compared to other compounds, even compounds with considerably higher log P values than the oxazolidinones listed therein. (Morozowich Declaration, paragraph 10).

Dr. Morozowich also points to data in Table 2 that further indicates that "chemical structure and log P are poorer predictors than expected of the degree to which other drugs can be solubilized by cyclodextrins." (Morozowich Declaration, paragraph 11). An example is provided of two related compounds, testosterone and D(-)-norgesterol, with very similar log P values (3.47 and 3.92, respectively) with significantly different solubilities in a 500 mg/ml solution of HPCD (38 mg/ml and 4/9 mg/ml, respectively). (*Id.*, citing data in Table 2). See paragraph 12 of the Morozowich Declaration for additional evidence, based upon the chemical structure of the orally active azole derivatives of Bartroli *et al.* and the chemical structure of oxazolidinones and cyclodextrins, why theoretical considerations would lead one of skill in the

art of the invention to expect solubilization of the azole derivatives, but not of the oxazolidinones by cyclodextrins.

In view of the evidence of surprising or unexpected results set forth in the Morozowich Declaration, Applicant respectfully traverses the rejection of claims 1-30, over Barbachyn *et al.* in view of Bartoli *et al.* Applicant, therefore, respectfully requests entry of the Morozowich Declaration, and withdrawal of the rejection.

II. SUMMARY

For reasons given above, Applicant respectfully requests that the present Remarks and Morozowich Declaration, submitted herein be entered, under 37 C.F.R. §1.113. Applicant submits, furthermore, that all of the claims remaining pending in the present case (i.e., claims 1-30) are in condition for allowance. Issuance of all the claims is, therefore, requested. The Examiner is invited to contact the undersigned at the telephone number given below, should she wish to discuss the present amendment and suggest changes to the claims in order to further prosecution of the application.

Dated: 4/30/03

Karen King

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